claims 1-6, 8-12, and 14-20 stand rejected. In this response, claims 1-2 have been amended. Applicants respectfully submit that the preceding Amendments and the following Remarks remove all grounds for rejection of the application, thereby placing it in condition for allowance.

Amendment of claims:

Claims 1-2 have been amended to more distinctly point out and claim the present invention. In particular, both claims have been amended to specify that the polymeric biomaterial elements within the claimed microarrays are *dry*. Support for this Amendment can be found throughout the specification as originally filed, e.g., see page 2, lines 18-22; page 7, lines 18-27; page 17, lines 6-12; page 23, lines 25-28; and page 25, line 8 to page 26, line 2. No new matter has been added by way of this Amendment.

As required, attached hereto is a marked-up version of the changes made to the claims by the current Amendment. The attached page is captioned "Appendix A - Version with markings to show changes made". For the Examiner's convenience, also attached hereto is a list of the pending claims as amended remaining in this application. The attached list is captioned "Appendix B - Claims pending after entrance of Amendment".

Rejection under 35 U.S.C. §112, ¶ 2:

The Examiner has rejected claim 12 under 35 U.S.C. §112, ¶ 2 as being indefinite. In particular, the Examiner asserts that:

> Claim 12 recites "drugs", "growth factors", "combinatorial compounds" and "adducts thereof, and mixtures thereof" in the Markush group. It is unclear what would or would not comprise each of the above members or "adducts thereof, and mixtures thereof". The specification does not provide a standard for ascertaining such terms, and thus one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant respectfully disagrees with the Examiner. The purpose of the claim definiteness requirement is to (a) ensure that the scope of the claims is clear so that the public is

informed of the boundaries of what constitutes infringement of the patent and (b) provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability. MPEP § 2173. Further, definiteness of claim language must be analyzed in light of (a) the content of the application disclosure, (b) the teachings of the prior art and (c) the claim interpretation that would be given by one possessing the ordinary level of skill in the art. MPEP § 2173.02.

With these guidelines in mind, Applicant first notes that the terms "drugs", "growth factors", "combinatorial compounds", "adducts" and "mixtures" are commonly used terms of art. One possessing the ordinary level of skill in the art would therefore be familiar with the common meaning and scope of these terms. Second, there is no teaching or suggestion in the application that Applicant intended the scope of these terms to be any different from the scope that they are commonly given in the art. Third, the application describes a variety of exemplary compounds, adducts, and mixtures that fall within and hence reinforce the scope that each of these terms are commonly given in the art (e.g., see page 12, lines 23-27 and page 13, line 9 to page 14, line 22).

Based on these facts there is no reason to believe that one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. Applicant thus respectfully requests that the indefiniteness rejection of claim 12 be withdrawn.

<u>Rejection under 35 U.S.C. §112, ¶ 1 for lack of written description:</u>

The Examiner has rejected claims 1-6, 8-12, and 14-20 under 35 U.S.C. §112, ¶ 1 for lack of written description. Applicant respectfully disagrees with the Examiner.

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Furthermore, there is a strong presumption that claims submitted with an application are adequately described by the application. *In re Wertheim* 541 F.2d 257 (CCPA 1976). The latter point is of particular importance in this case since all of the claims that stand rejected for lack of written description were present in the application as originally filed. Therefore, the burden is on the Examiner to overcome the strong presumption of descriptive support with

evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Examiner has not, and cannot meet this burden; the claimed invention is appropriately described in the specification.

In particular, the present specification clearly puts the public on notice that, at the time of filing, Applicant had invented a broadly applicable method for preparing microarrays of polymeric biomaterials. The written description explicitly states that the invention encompasses microarrays that include a variety of bases, cytophobic surfaces, and polymeric biomaterials. The specification also describes the use of specific bases that are recited in claim 3 (e.g., see page 5, lines 18-19 and the Examples). Likewise, the specification describes the use of specific cytophobic surfaces as recited in claims 4-6 (e.g., see page 6, line 3 to page 7, line 27 and the Examples) and specific polymeric biomaterials as recited in claims 8-11 (e.g., see page 7, line 28 to page 12, line 7 and the Examples). The specification also points to compounds having the characteristics recited in claims 12 and 14 (e.g., see page 12, line 8 to page 14, line 22). Finally, the specification describes the spacing and density limitations of claims 15-20 (e.g., see page 15, line 9 to page 16, line 2 and the Examples).

The Examiner provides no evidence or reason to believe that a skilled person would not reasonably conclude that the inventors were in possession of the claimed genus or species. The fact that certain species within the claimed genus have not been prepared does not weaken Applicant's position – it is well accepted that every species in a genus need not be described, let alone reduced to practice, in order that a genus meet the written description. *Utter v. Hiraga* 845 F.2d 993 (Fed. Cir. 1988). The present specification and claims as originally filed clearly put the public on notice that the inventors considered the pending claims to be within the scope of their invention; further description is neither necessary nor appropriate.

<u>Rejection under 35 U.S.C. §112, ¶ 1 for lack of enablement:</u>

The Examiner has rejected claims 12 and 14 under 35 U.S.C. §112, ¶ 1 for lack of enablement. Applicant respectfully disagrees with the Examiner.

A specification must teach those of ordinary skill in the art to make and use the claimed invention. The description in the specification must provide sufficient guidance that no more than routine experimentation is required to practice the claimed invention. *In re Angstadt*, 537

F.2d 489, (CCPA 1976). Factors to be considered in analyzing the sufficiency of a disclosure include:

(1) the breadth of the claims;

(2) the nature of the invention;

(3) the state of the prior art;

(4) the level of skill of one of ordinary skill;

(5) the level of predictability in the art;

(6) the amount of direction provided by the inventor;

(7) the existence of working examples; and

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, (Fed. Cir. 1988).

Claim 12 recites "a microarray wherein at least one of said polymeric biomaterials further comprises a compound". Claim 14 further specifies that "said compound is non-covalently bound to the synthetic polymer component or components of the polymeric biomaterial". The claims are broad. However, such breadth is appropriate in the context of the present invention.

Applicant has invented a broadly applicable method for preparing microarrays of polymeric biomaterials. The method comprises (see page 2, lines 19-22):

(1) providing a base with a cytophobic surface,

(2) providing polymeric biomaterials as stock solutions in a suitable solvent,

(3) depositing the polymeric biomaterials as discrete elements of a microarray on the cytophobic surface, and

(4) removing the solvent by drying the microarray in a vacuum.

The polymeric biomaterials include one or more synthetic polymers (e.g., see page 2, line 29 to page 3, line 9). Applicant has successfully shown that the polymeric biomaterials can include a range of synthetic polymers and that the methods are relatively insensitive to the chemical composition and/or combination of synthetic polymers (e.g., see the Examples). Separately and as discussed at great length in the present application, a significant body of literature existed in the art as of the present application's filing date that described methods for combining synthetic or natural compounds with a variety of synthetic polymers (e.g., by covalent and non-covalent association as described on page 12, line 8 to page 14, line 19 or by

mixing and encapsulation as described on page 14, lines 19-22). The present inventors have connected these bodies of knowledge with their inventive method by recognizing that synthetic polymer-compound combinations could be used as starting materials instead of (or in combination with) plain synthetic polymers. Once the connection has been made, researchers of ordinary skill can draw upon the methods provided in the present application and the established knowledge in the prior art.

With respect to the state of the prior art, there is no prior art relating to the microarrays of claims 12 and 14 (see below for a discussion of Schreiber et al.). Prior to the present invention, it simply had not been considered. As mentioned above, the prior art does however describe a variety of methods for preparing a range of synthetic polymer-compound combinations (e.g., see page 12, line 8 to page 14, line 22).

The level of skill in this art is very high, practitioners typically have Ph.D. degrees. The Examiner has acknowledged this (see page 6, lines 10-13 of the Office Action).

With respect to the level of predictability in the art and the amount of direction provided by the inventors, the Examiner states that the specification gives no guidance to permit one of skill in the art to devise strategies for binding any "compound" to a microarray of polymeric biomaterial elements. Applicant respectfully disagrees. First, the specification clearly states that microarrays that include synthetic or natural compounds are to be prepared in exactly the same way as microarrays that lack these compounds, the only difference stems from a change in starting materials. Bearing this in mind, the specification points to numerous methods for preparing these different starting materials that were well known at the time of filing. Thus, the inventors provided significant guidance. The Examiner further states that further research would be necessary, to make or use such a system as the practice of such would not be predictable. Again, Applicant disagrees. The specification indicates that the inventive methods are relatively independent of the chemical composition of the polymeric biomaterials. In particular, microarrays of polymeric biomaterials have been prepared using a range of combinations of synthetic polymers having a variety of chemical compositions (e.g., see the Examples). Applicant therefore submits that the level of predictability is relatively high for this particular invention.

Finally, with respect to the quantity of experimentation required in light of the content of

the specification and the nature of the invention, Appellant submits that the quantity would be reasonably low. As discussed above, the specification identifies a large number of natural and synthetic compounds that have been associated with synthetic polymers. These and other polymer-compound combinations known in the art could be readily tested using the few simple steps of the inventive method, namely (1) dissolving the polymer-compound combinations in a solvent, (2) depositing the polymer-compound combinations as discrete microarray elements on a cytophobic surface, and (3) removing the solvent by drying the microarray in a vacuum. The present application describes a variety of automated high throughput methods that could be used to perform these tests with a minimal amount of experimentation (e.g., see page 14, line 23 to page 17, line 12). For all of these reasons, Appellant respectfully submits that pending claims 12 and 14 are fully enabled by the specification.

Rejection under 35 U.S.C. §102(b):

The Examiner has rejected claims 1-6, 8-11 and 15-20 under 35 U.S.C. §102(b) as being anticipated by Schreiber et al. (WO 98/16830). Applicant respectfully disagrees with the Examiner.

In order to anticipate claims 1-6, 8-11 and 15-20, Schreiber et al. must teach each and every element of the claims. MPEP § 2131. As amended, claims 1 and 2 of the present application (and claims 3-6, 8-11 and 15-20 that depend therefrom) specify that the polymeric biomaterial elements within the claimed microarrays are *dry*. Schreiber et al. does not teach an array of *dry* polymeric biomaterial elements. Instead and as noted by the Examiner, Schreiber et al. teaches quite the opposite, namely an array of *droplets* (e.g., see page 5, lines 8-23). The droplets include test compounds and the array is used in an assay system that is dependent on both the integrity and isolation of the droplets (e.g., see page 2, lines 5-10; page 9, lines 24-26; and page 10, line 30 to page 11, line 2). In particular, Schreiber et al. emphasizes that the assay system is designed to minimize droplet evaporation (e.g., see page 10, lines 14-18). In the absence of any teaching of an array of *dry* polymeric biomaterial elements and in view of the fact that Schreiber et al. effectively teaches away from such an array, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1-6, 8-11 and 15-20 under 35 U.S.C. §102(b) over Schreiber et al.

Conclusion

Based on the arguments presented above, it is submitted that the pending claims, as amended herein, are allowable over the art of record. Applicants would like to thank the Examiner for her thoughtful comments and careful consideration of the case. If a telephone conversation would help expedite prosecution of this case, please do not hesitate to contact the undersigned at (617) 248-4793. Additionally, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,

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Limited Recognition Under 37 CFR §10.9(b)

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Dated: January 28, 2003

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January 28, 2003 — Linda M. Amato
Date — Signature

Linda M. Amato
Typed or Printed Name of person signing certificate

Appendix A – Version with markings to show changes made

In the claims:

Claims 1 and 2 have been amended as follows:

1. (Once amended) A microarray of polymeric biomaterials comprising:

    a base comprising a cytophobic surface; and

    a plurality of discrete dry polymeric biomaterial elements non-covalently bound to said cytophobic surface.

2. (Once amended) A microarray of polymeric biomaterials comprising:

    a base comprising a cytophobic surface; and

    a plurality of discrete dry non-monolayer polymeric biomaterial elements bound to said cytophobic surface.

Appendix B – Claims pending after entrance of Amendment

1. (Once amended) A microarray of polymeric biomaterials comprising:

   a base comprising a cytophobic surface; and

   a plurality of discrete dry polymeric biomaterial elements non-covalently bound to said cytophobic surface.

2. (Once amended) A microarray of polymeric biomaterials comprising:

   a base comprising a cytophobic surface; and

   a plurality of discrete dry non-monolayer polymeric biomaterial elements bound to said cytophobic surface.

3. The microarray of claim 1 or 2, wherein said base comprises a material selected from the group consisting of glass, plastic, metal, ceramic, and combinations thereof.

4. The microarray of claim 1 or 2, wherein said cytophobic surface comprises a hydrogel.

5. The microarray of claim 4, wherein said hydrogel comprises a polymer selected from the group consisting of homopolymers of methacrylic acid esters, homopolymers of alkylene oxides, homopolymers of alkylene glycols, copolymers thereof, and mixtures thereof.

6. The microarray of claim 4, wherein said hydrogel comprises a polymer selected from the group consisting of poly(methyl methacrylate), poly(isobutyl methacrylate), poly(pentyl methacrylate), poly(2-hydroxy-ethyl methacrylate), copolymers thereof, and mixtures thereof.

7. The microarray of claim 4, wherein said hydrogel comprises a polymer selected from the group consisting of poly(ethylene oxide), poly(propylene 1,2-glycol), poly(propylene 1,3-glycol), copolymers thereof, and mixtures thereof.

8. The microarray of claim 1, wherein said polymeric biomaterial elements are bound to said cytophobic surface via a non-covalent interaction selected from the group consisting of chemical adsorption, hydrogen bonding, surface interpenetration, ionic bonding, van der Waals forces, hydrophobic interactions, magnetic interactions, dipole-dipole interactions, and combinations thereof.

9. The microarray of claim 2, wherein said polymeric biomaterial elements are bound to said cytophobic surface via an interaction selected from the group consisting of chemical adsorption, hydrogen bonding, surface interpenetration, covalent bonding, ionic bonding, van der Waals forces, hydrophobic interactions, magnetic interactions, dipole-dipole interactions, and combinations thereof.

10. The microarray of claim 1 or 2, wherein each of said polymeric biomaterial elements comprises at least one polymer selected from the group consisting of synthetic polymers, adducts thereof, and mixtures thereof.

11. The microarray of claim 10, wherein said synthetic polymers are selected from the group consisting of polyamides, polyphosphazenes, polypropylfumarates, synthetic poly(amino acids), polyethers, polyacetals, polycyanoacrylates, polyurethanes, polycarbonates, polyanhydrides, poly(ortho esters), polyhydroxyacids, polyesters, polyacrylates, ethylene-vinyl acetate polymers, cellulose acetates, polystyrenes, poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl imidazole), poly(vinyl alcohol), and chlorosulphonated polyolefins.

12. The microarray of claim 10, wherein at least one of said polymeric biomaterial elements further comprises a compound selected from the group consisting of drugs, growth factors, combinatorial compounds, proteins, polysaccharides, polynucleotides, lipids, adducts thereof, and mixtures thereof.

13. The microarray of claim 12, wherein said compound is covalently bound to the synthetic

polymer component or components of the polymeric biomaterial.

14. The microarray of claim 12, wherein said compound is non-covalently bound to the synthetic polymer component or components of the polymeric biomaterial.

15. The microarray of claim 1 or 2, wherein each of said polymeric biomaterial elements are between 10 and 1000 μm in diameter.

16. The microarray of claim 1 or 2, wherein each of said polymeric biomaterial elements are between 50 and 500 μm in diameter.

17. The microarray of claim 1 or 2, wherein said polymeric biomaterial elements are disposed at between 100 and 1200 μm intervals in a rectangular microarray.

18. The microarray of claim 1 or 2, wherein said polymeric biomaterial elements are disposed at between 300 and 500 μm intervals in a rectangular microarray.

19. The microarray of claim 1 or 2, wherein said polymeric biomaterial elements are present at a density on said cytophobic surface that ranges from 1 to 1,000 polymeric biomaterial elements per cm^2.

20. The microarray of claim 1 or 2, wherein said polymeric biomaterial elements are present at a density on said cytophobic surface that ranges from 10 to 100 polymeric biomaterial elements per cm^2.

21. A method for the high throughput screening of polymeric biomaterials for their ability to affect cellular behavior comprising:

providing a microarray of polymeric biomaterial elements that are bound to a cytophobic surface;

contacting said microarray with a cell culture for a period of time sufficient to

allow the cells to adhere to said polymeric biomaterial elements; and

assaying the cellular behavior for each polymeric biomaterial element of the microarray.

22. The method of claim 21, wherein said cytophobic surface comprises a hydrogel.

23. The method of claim 22, wherein said hydrogel comprises a polymer selected from the group consisting of homopolymers of methacrylic acid esters, homopolymers of alkylene oxides, homopolymers of alkylene glycols, copolymers thereof, and mixtures thereof.

24. The method of claim 22, wherein said hydrogel comprises a polymer selected from the group consisting of poly(methyl methacrylate), poly(isobutyl methacrylate), poly(pentyl methacrylate), poly(2-hydroxy-ethyl methacrylate), copolymers thereof, and mixtures thereof.

25. The method of claim 22, wherein said hydrogel comprises a polymer selected from the group consisting of poly(ethylene oxide), poly(propylene 1,2-glycol), poly(propylene 1,3-glycol), copolymers thereof, and mixtures thereof.

26. The method of claim 21, wherein said polymeric biomaterial elements are non-covalently bound to said cytophobic surface.

27. The method of claim 26, wherein said polymeric biomaterial elements are bound to said cytophobic surface via a non-covalent interaction selected from the group consisting of chemical adsorption, hydrogen bonding, surface interpenetration, ionic bonding, van der Waals forces, hydrophobic interactions, magnetic interactions, dipole-dipole interactions, and combinations thereof.

28. The method of claim 21, wherein said polymeric biomaterial elements are not monolayers.

29. The method of claim 21, wherein each of said polymeric biomaterial elements comprises at least one polymer selected from the group consisting of synthetic polymers, adducts thereof, and mixtures thereof.

30. The method of claim 29, wherein said synthetic polymers are selected from the group consisting of polyamides, polyphosphazenes, polypropylfumarates, synthetic poly(amino acids), polyethers, polyacetals, polycyanoacrylates, polyurethanes, polycarbonates, polyanhydrides, poly(ortho esters), polyhydroxyacids, polyesters, polyacrylates, ethylene-vinyl acetate polymers, cellulose acetates, polystyrenes, poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl imidazole), poly(vinyl alcohol), and chlorosulphonated polyolefins.

31. The method of claim 29, wherein at least one of said polymeric biomaterial elements further comprises a compound selected from the group consisting of drugs, growth factors, combinatorial compounds, proteins, polysaccharides, polynucleotides, lipids, adducts thereof, and mixtures thereof.

32. The method of claim 31, wherein said compound is covalently bound to the synthetic polymer component or components of the polymeric biomaterial.

33. The method of claim 31, wherein said compound is non-covalently bound to the synthetic polymer component or components of the polymeric biomaterial.

34. The method of claim 21, wherein said polymeric biomaterial elements are between 10 and 1000 μm in diameter.

35. The method of claim 21, wherein said polymeric biomaterial elements are between 50 and 500 μm in diameter.

36. The method of claim 21, wherein:

said microarray is a rectangular microarray; and

said polymeric biomaterial elements are disposed at between 100 and 1200 μm intervals on said cytophobic surface.

37. The method of claim 21, wherein:

said microarray is a rectangular microarray; and

said polymeric biomaterial elements are disposed at between 300 and 500 μm intervals on said cytophobic surface.

38. The method of claim 21, wherein said polymeric biomaterial elements are present at a density on said cytophobic surface that ranges from 1 to 1,000 polymeric biomaterial elements per cm^2.

39. The method of claim 21, wherein said polymeric biomaterial elements are present at a density on said cytophobic surface that ranges from 10 to 100 polymeric biomaterial elements per cm^2.

40. The method of claim 21, wherein said cells are selected from the group consisting of mammalian cells, bacterial cells, yeast cells, and plant cells.

41. The method of claim 21, wherein said cells are selected from the group of mammalian cells consisting of chondrocytes, fibroblasts, connective tissue cells, epithelial cells, endothelial cells, cancer cells, hepatocytes, islet cells, smooth muscle cells, skeletal muscle cells, heart muscle cells, kidney cells, intestinal cells, organ cells, lymphocytes, blood vessel cells, stem cells, human embryonic stem cells, and mesenchymal stem cells.

42. The method of claim 21, wherein the step of assaying comprises assaying for cellular proliferation.

43. The method of claim 21, wherein the step of assaying comprises assaying for cellular differentiation.

44. The method of claim 21, wherein the step of assaying comprises assaying for gene expression.

45. A method of preparing a microarray of polymeric biomaterials comprising:

providing a base comprising a substrate surface;

providing polymeric biomaterials in a solvent selected from the group consisting of dimethylformamide, dimethylsulfoxide, chloroform, and dichlorobenzene; and

depositing said polymeric biomaterials as a plurality of discrete elements on said substrate surface using a robotic liquid handling device, wherein

said polymeric biomaterials are dissolved at a concentration of between 10 and 200 mg/ml in said solvent, and said substrate surface comprises a hydrogel.

46. The method of claim 45, wherein said liquid handling device deposits via pin fluid deposition.

47. The method of claim 45, wherein said liquid handling device deposits via syringe pumped fluid deposition.

48. The method of claim 45, wherein said liquid handling device deposits via piezoelectric fluid deposition.

49. The method of claim 45, wherein said polymeric biomaterial elements are deposited as drops of between 0.1 and 100 nl.

50. The method of claim 45, wherein said polymeric biomaterial elements are deposited as drops of between 1 and 10 nl.

51. A method for the high throughput screening of compounds for their ability to affect cellular behavior comprising:

providing a microarray of polymeric biomaterial elements arranged on a cytophobic surface;

contacting said polymeric biomaterial elements with a cell culture for a period of time sufficient to allow the cells to adhere to said polymeric biomaterial elements; and

assaying the cellular behavior for each polymeric biomaterial element of the microarray, wherein:

at least one of said polymeric biomaterial elements comprises one of said compounds.

52. The method of claim 51, wherein said compounds are drugs.

53. The method of claim 51, wherein said compounds belong to a synthetic combinatorial library of compounds

54. The method of claim 51, wherein said compounds are selected from the group consisting of proteins, polysaccharides, polynucleotides, lipids, adducts thereof, and mixtures thereof.